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An International Association For Pharmaceutical Science And Technology

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US Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Ref.: [Docket No. 03D-0386, CDER 2003131]
Draft Guidance for Industry – Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice.

Dear Sir/Madam:

PDA is pleased to provide these comments on the Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality.

Comments:

Point #1
Assuring Issues Are Raised During an Inspection

The Guidance is very clear in the Agency's expectations that this process does not preclude, eliminate, or diminish the communication of issues between the firm and the inspector during the inspection. PDA supports the open communication and sees it as necessary to move the inspection into a learning experience. However, the Agency must recognize there are legitimate instances where issues are not discussed. Even where both parties agree to daily discussions of open issues, there can be issues where inspectors do not discuss an issue as an observation due to many different reasons. There also may be instances where firms are reticent to discuss contentious issues. The element of time, more than personal style, may be the major contributing factor. However, fears of retribution, ranging from negative attitudes to more severe inspectional techniques, are a valid concern on the part of a firm. There may be issues that are **not** raised during the course of an inspection that a firm may want to bring forward as part of the scientific and technical dispute resolution process. PDA feels the firms should be allowed to appeal as part of the dispute resolution process, if they can provide sound reasons for why this issue was not reviewed during the inspection.

Point #2
Composition of the Dispute Resolution Panel

Issues raised to the Tier 2 Dispute Resolution Panel will, by design, be technical in nature. Additionally, it should not be forgotten the issues are being raised, to this level, above the opinion of the inspector and ORA (both at the district and at the center level). Impartiality and broad scientific knowledge must be a cornerstone in determining the selection of the panel.

PDA feels strongly that the Dispute Resolution Panel must include panel members outside of the Agency. Impartial expertise can be provided by other knowledgeable experts outside of the agency. Professional organizations, such as the PDA, can compile a list of pre-qualified experts in the spectrum of technologies involved who can be available for participation on the Dispute Resolution Panel.

Point #3
Disclosure of Information

As part of a response to an inspectional observation in the existing process, companies have provided information which is redacted upon public disclosure. Companies, through the benefit of time and experience, are "calibrated" to know how much and which information to provide and through the benefit of a development of trust, know how the Agency will disseminate the information.

Raising an issue as part of the Tier 1 technical dispute process will, in all likelihood, require more information than normally contained within a response to an inspectional observation submitted to the Agency. Additionally, the Agency will face a difficult decision: how much information to release to sufficiently explain the issue and the decision from the dispute balanced against the need to maintain the confidentiality of the proprietary information.

For an issue to be elevated into the Tier 2 Dispute Resolution Panel, even more detailed information will need to be forwarded by the company to the Agency. Any correspondence between the Agency and the firm will also be subject to disclosure. The confidentiality measures to be employed must be of the highest order and should be discussed between the Agency and the firm. At a minimum, the Agency must afford the company an opportunity to review and first comment regarding what the agency intends to disclose.

Point #4
Pending Regulatory Action during Interim Periods

It seems inappropriate to take regulatory action while the dispute resolution process is underway. However, it is understandable there may be rare cases, in the interest of public health, where prompt regulatory action is necessary. While there is a pending dispute resolution, the Guidance should clarify the conditions under which the Agency will forestall regulatory action and clarify the conditions under which the Agency will proceed with further regulatory action.

Point #5
Timing
There is a lack of consistency in time frames as specified in the Guidance. The Agency has stated it has "generally thirty days" to respond the firm if the Agency disagrees with the firm's request at the Tier 1 level. Further, the Agency can delay a response, albeit with a communication to the firm, without defining a time frame for completion of the request. PDA anticipates that responses from the Agency will be completed in the given thirty days and suggests that in the rare circumstances where additional time is required, a maximum time of sixty days be set as the limit.

As an issue progresses into the Tier 2 Process with the need for convening a Dispute Resolution Panel, time frames are not clearly stipulated. Once a determination has been made that an issue warrants review at this level, it will be reviewed at the next meeting for which there is sufficient time on the agenda. While PDA commends the Agency for assuring each issue is given the proper attention and time it deserves, there is concern of the potential for substantial delays in the process. Related to this concern, is how the Agency will proceed with further regulatory actions as a result of the inspectional observations (see discussion on Point #4 above).

Point #6
The Dispute Resolution Process as a Learning Tool for both the Agency and Industry

The Agency's position on whether the decisions reached by this process will set a precedent for other similar situations should be made clear. PDA would like to suggest there be a procedure for circulating the information within the Agency as training on the issues and the scientific decisions. Included in this process would be clarification if these decisions effect in practice a change of rules. This can in fact, lead to consistency in the interpretation of regulations by inspectors in the field.

After appropriate redaction, the information from these disputes is invaluable as a learning tool for industry as well.

Statement from Guidance, Line 20
This document is intended to provide guidance to manufacturers of veterinary and human drugs, including human biological drug products, on how to resolve disputes of scientific and technical issues relating to current good manufacturing practice (CGMP) requirements.

Comments
There is no mention of medical devices (CDRH). Please clarify how the guidance applies to drug/device combination products. E.g., would observations related to OSR interpretation on the device aspects be eligible for the process? Our recommendation is to have this guidance apply to all combination products.

Statement from Guidance, Line 32
Manufacturers may seek clarification of scientific or technical issues with the inspection team at any time during an inspection.

Comments
PDA proposes to add that a firm can hold a discussion with the relevant FDA Office of Compliance (CBER, CDER) at any time during the inspection to resolve a GMP issue disagreement between the company and inspectors prior to the issuance of a 483 citation concerning the scientific basis for the disputed interpretation of the GMP observation.

Statement from Guidance, Line 93
At the conclusion of an inspection, investigators usually meet with the manufacturer's management to again discuss observations and solicit views and additional relevant information. These processes are described in detail in the Investigations Operations Manual (IOM) Sections 512 and 516, as listed in Section I of this document.

Comments
Please replace "usually" with "are obligated by agency policy to offer to".

Statement from Guidance, Line 154
The ORA unit will issue a written response to the manufacturer within 30 days of receipt of the request, noting its agreement with the manufacturer and resolution of the dispute. The resolution may take the form of a letter. It may also take the form of...

Comments
Please change " it may also take the form of an addendum to the existing Form FDA 483" to "Any such written response will be considered to be an addendum to the 483, and shall be publicly disclosed, with appropriate purging, in the event of any disclosure."

Statement from Guidance, Line 158
All disputes resolved at the ORA level will be copied to the relevant program center for information and public dissemination.

Comments
Please add after public dissemination "with appropriate redaction, in accordance with applicable requirements."

Statement from Guidance, Line 164
Responses that disagree with a manufacturer's position will incorporate a review and decision by the relevant program center, which may require additional time as described below.

Comment
Please change "review and decision" to "review of the decision".

Statement from Guidance, Line 186
The DR Panel resides at the Agency level.

Comment
Please clarify at which level in the Agency the DR Panel resides. PDA recommends the Agency Level specified is that of the Commissioner.

Statement from Guidance, Line 234
No new information should be submitted as part of a request for formal dispute resolution. If a manufacturer presents new information about an issue in requesting formal dispute resolution, the matter will be returned to the ORA unit for review as appropriate.

Comment
There may be the instance during the inspection where a firm does not understand the investigator's question, and therefore not provide information available at the time of inspection. Then, the administrative record will not contain this information. If in reviewing the observation, the firm understands the observation and realizes that this information would dispute the observation, the firm should have the ability to submit this information as part of their dispute.

If you have any questions regarding our comments, or how we may assist with further development of the Guidance, please contact me.

Sincerely,

Victoria Ann Dedrick

Victoria A. Dedrick
Vice President, Quality & Regulatory Affairs